(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 September 2005 (29.09.2005)

PCT

(10) International Publication Number
WO 2005/090319 A1

(51) International Patent Classification[7]: C07D 243/24

(21) International Application Number:
PCT/GB2005/001050

(22) International Filing Date: 21 March 2005 (21.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0406280.8	19 March 2004 (19.03.2004)	GB
0406282.4	19 March 2004 (19.03.2004)	GB
0423462.1	21 October 2004 (21.10.2004)	GB

(71) Applicant *(for all designated States except US)*: **ARROW THERAPEUTICS LIMITED** [GB/GB]; Britannia House, 7 Trinity Street, London SE1 1DA (GB).

(72) Inventors; and

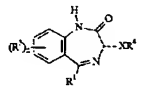
(75) Inventors/Applicants *(for US only)*: **DOWDELL, Verity** [GB/GB]; c/o Arrow Therapeutics Limited, Britannia House, 7 Trinity Street, London SE1 1DA (GB). **KELSEY, Richard, David** [GB/GB]; c/o Arrow Therapeutics Limited, Britannia House, 7 Trinity Street, London SE1 1DS (GB). **CARTER, Malcolm** [GB/GB]; c/o Arrow Therapeutics Limited, Britannia House, 7 Trinity Street, London SE1 1DS (GB). **HENDERSON, Elisa, Ann** [GB/GB]; c/o Arrow Therapeutics Limited, Britannia House, 7 Trinity Street, London SE1 1DS (GB).

(74) Agent: **SRINIVASAN, Ravi, Chandran**; J.A. Kemp & CO, 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

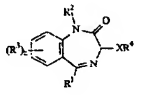
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

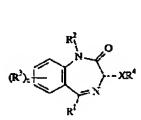
(54) Title: PROCESS FOR PREPARING BENZODIAZEPINES



(I)



(IIa)



(II)

(57) Abstract: A process for producing a compound which is a benzodiazepine derivative of formula: (I) wherein: represents or R^1 represents C_{1-6} alkyl, aryl or heteroaryl; each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R′ and R″ is the same or different and represents hydrogen or C_{1-6} alkyl; n is from 0 to 3; X represents -NH-, $-N(C_1-C_6alkyl)-$, -CO-, $-CO-NR'-$, -S(O)- or $-S(O)_2-$, wherein R′ is hydrogen or a C_1-C_6 alkyl group; and R^4 represents hydrogen; or $-CO-R_4'$ or $-CO-NH-R^{4'}$, wherein $R^{4'}$ is a C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group, which group is substituted by a C_1-C_6 hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group or a $-(C_1-C_4$ alkyl)$-X_1-(C_1-C_4alkyl)-X_2-(C_1-C_4$ alkyl) group, wherein X_1 represents -O-, -S- or $-NR'-$, wherein R′ represents H or a C_1-C_4 alkyl group and X_2represents -CO-, -SO- or $-SO_2-$; or $R^{4'}$ represents $-A_1-Y-A_2$, wherein: A_1 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; Y represents a direct bond or a C_1-C_4 alkylene, $-SO_2-$, -CO-, -O-, -S or $-NR'-$, wherein R′ is a C_1-C_6alkyl group; and A_2 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; or R^4 is a group selected from aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- and $-ZR^5$, wherein: Z represents -CO-, -S(O)- or $-S(O)_2-$; and R^5 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)-, aryl-(C_{1-6} alkyl)-O-, heteroaryl-(C_{1-6}alkyl)-O-, carbocyclyl-(C_{1-6} alkyl)-O-, heterocyclyl-(C_{1-6} alkyl)-O- or $-NR'R''$ wherein each R′ and R″ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6}alkyl)-, carbocyclyl-(C_{1-6} alkyl)- or heterocyclyl-(C_{1-6} alkyl)-; or a pharmaceutically acceptable salt thereof; which process comprises: (a) subjecting a racemic benzodiazepine derivative of formula: (IIa): wherein R^1, R^3, R^4, n and X are as defined above, and R^2 represents an amino protecting group, to crystallisation induced dynamic resolution to yield a benzodiazepine derivative of formula (II): wherein, R^1, R^2, R^3, R^4, n and X are as defined above; and (b) deprotecting the benzodiazepine derivative of formula (II) as defined above to yield a benzodiazepine derivative of formula (I) or a pharmaceutically acceptable form thereof as defined above.

WO 2005/090319 A1

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.